

REMARKS

I. Status of the Claims

Claims 29, 30, 32-39, 43-51 and 58 are pending and stand rejected, variously, under 35 U.S.C. §112, first paragraph and §103. The specific ground for rejection, and applicants' response thereto, are set out in detail below.

II. Interview

Applicants wish the that Examiner Nguyen for the courtesy of a telephonic interview held on July 24, 2007. Though agreement was not reached, it is believed that the interview advanced the prosecution.

III. Rejection Under 35 U.S.C. §112, First Paragraph

Claims 29, 30, 32-39, 43-35, 47-51 and 58 stand is rejected under the first paragraph of §112 as lacking enablement. According to the examiner, the claims are only enabling for both the first and second DNA segments being stably integrated in the genome of the cell. In support of this position, it is argued that the only support for foreign DNA being stably integrated in on page 28, lines 24-28, which allegedly shows both sequences in the same substrate vector. It is also argued that not all integration into a host cell genome is *stable* integration. Applicants traverse.

First, applicants must point out that the invention is drawn, in one aspect, to the *integration* of a DNA segment into a host cell genome. As such, it is necessary that at some point in the method, there be an *unintegrated DNA segment*. At present, claim 29 recites that the first DNA segment is integrated prior to the second DNA segment. Because of the existence

of appropriate *att* sequences in both (a) the integrated first DNA segment, and (b) the non-integrated second DNA segment, the second DNA segment will be inserted into the genome of the host cell. This embodiment is clearly supported at page 10 of the specification: “The introduction of the first and second DNA sequence with or without further DNA sequences *may be performed both consecutively* and in a co-transformation wherein the DNA sequences are present on two different DNA molecules.” Emphasis added.

Second, the examiner is, of course, also incorrect in stating that page 28 provides the only discussion of stable integration of foreign DNA. There are numerous statements throughout the specification that discuss this event. Regardless, as shown above, integration of a first DNA segment, followed by integration of a second DNA segment, clearly is supported by the specification as filed. Applicants also point to original claim 2 as support for this aspect of the invention.

Third, the examiner seems to focus on the examples, where both *att* sequences are found integrated into the host cell prior to Int action. While it is certainly true that some embodiments take this form, this is not required, and the specification clearly contemplates (see above) that only one DNA segment be found integrated into the genome prior to Int action and introduction of a second DNA segment.

Fourth, the examiner argues that not all integration is “stable.” Whether or not true, applicants point out that the term “stable” has been removed from claim 29, thereby rendering the comment moot.

Reconsideration and withdrawal of the rejection, in light of the preceding comments, is therefore respectfully requested.

IV. Rejections Under 35 U.S.C. §103

A. **Crouzet *et al.* and Christ & Dröge**

Claims 29, 30, 32, 33, 36, 38, 44-48 and 58 remain rejected over the combined disclosures of Crouzet *et al.* and Christ & Dröge. The examiner states that the skilled artisan would have modified the method taught by Crouzet *et al.* by utilizing the mutant *lambda* integrases Int-h and Int-h/218 described in Christ & Dröge for their method of generating chimeric DNA. Applicants traverse.

As has been argued over and over, Crouzet *et al.* worked with wild-type integrases in eukaryotic cells, and Christ & Dröge worked in prokaryotic systems, albeit with mutant integrase. Yet the examiner continues to ignore the fact that there was no *a priori* expectation of success, even if motivation for combining these two very distinct systems is presumed. Rather, the examiner simply states that “an ordinary skilled artisan would have a reasonable expectation of success in light of the cited references. As a matter of *law*, such a statement is legally insufficient to establish obviousness, *particularly* in light of the countervailing declaratory evidence:

The legal concept of *prima facie* obviousness is a procedural tool of examination which applies broadly to all arts. It allocates who has the burden of going forward with production of evidence in each step of the examination process. See *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976); *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972); *In re Saunders*, 444 F.2d 599, 170 USPQ 213 (CCPA 1971); *In re Tiffin*, 443 F.2d 394, 170 USPQ 88 (CCPA 1971), *amended*, 448 F.2d 791, 171 USPQ 294 (CCPA 1971); *In re Warner*, 379 F.2d 1011, 154 USPQ 173 (CCPA 1967), *cert. denied*, 389 U.S. 1057 (1968). ***The examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness.*** If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness. If, however, the examiner does produce a *prima facie* case, the burden of coming forward

with evidence or arguments shifts to the applicant who may submit additional evidence of nonobviousness, such as comparative test data showing that the claimed invention possesses improved properties not expected by the prior art. *The initial evaluation of prima facie obviousness thus relieves both the examiner and applicant from evaluating evidence beyond the prior art and the evidence in the specification as filed until the art has been shown to suggest the claimed invention.*

To reach a proper determination under 35 U.S.C. 103, the examiner must step backward in time and into the shoes worn by the hypothetical “person of ordinary skill in the art” when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention “as a whole” would have been obvious at that time to that person. Knowledge of applicant's disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the “differences,” conduct the search and evaluate the “subject matter as a whole” of the invention. The tendency to resort to “hindsight” based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art....

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *Second, there must be a reasonable expectation of success.* Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art,* and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143 - § 2143.03 for decisions pertinent to each of these criteria

When an applicant submits evidence, whether in the specification as originally filed or in reply to a rejection, the examiner must reconsider the patentability of the claimed invention. The decision on patentability must be made based upon consideration of *all the evidence*, including the evidence submitted by the examiner and the evidence

submitted by the applicant. A decision to make or maintain a rejection in the face of all the evidence must show that it was based on the totality of the evidence. Facts established by rebuttal evidence must be evaluated along with the facts on which the conclusion of obviousness was reached, not against the conclusion itself. *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990).

MPEP §2142 (emphasis added). Here, the examiner simply cites to the references generally and to the “skill in the art” – those are not “evidence,” and are not sufficient to establish a *prima facie* case. Moreover, the examiner has dismissed evidence provided by applicants, and instead substituted his own unsupported conclusions on expectation of success.¹

Thus, for the reasons set forth above, reconsideration and withdrawal of this rejection is again requested.

B. Crouzet *et al.*, Christ & Dröge, and Capecchi *et al.*

Claims 29 and 43 remain rejected over Crouzet *et al.*, Christ & Dröge and Capecchi *et al.* Applicants traverse.

Just as with the previous rejections, applicants submit that the rejection here fails for lack of motivation and lack of an expectation of success. The defects of Crouzet *et al.* and Christ & Dröge have been discussed above and will not be repeated here. Capecchi *et al.*, which simply is cited for a “positive-negative selector vector,” fails to address the issue of whether modified integrases would work in eukaryotic cells, as set out in detail above. Thus, again, there was no motivation for combining the primary and secondary references, and even if there were, there was no likelihood of success that they would work together.

¹ Initially, the examiner dismissed this evidence on the grounds that the claims were too broad in scope to be commensurate with the declarants’ argument (see Final OA dated Dec. 14, 2006, pp. 7 & 9). However, once applicants amended the claims to address the examiner’s concerns, the declaration was simply ignored.

Thus, for the reasons set forth above, reconsideration and withdrawal of this rejection also is respectfully requested.

C. Crouzet *et al.*, Christ & Dröge, and Hartley *et al.*

Claims 29, 34-37 and 39 stand rejected over Crouzet *et al.*, Christ & Dröge and Hartley *et al.* Applicants traverse.

Just as with the previous rejections, applicants submit that the rejection here fails for lack of motivation and lack of an expectation of success. The defects of Crouzet *et al.* and Christ & Dröge have been discussed above and will not be repeated here. Hartley *et al.*, which teaches recombinational methods in prokaryotic and eukaryotic host cells using, *inter alia*, the lambda integrase recombination system with exclusively the *wild-type* lambda integrase, fails to address the issue of whether *modified* integrases would work in eukaryotic cells, as set out in detail above. Thus, again, there was no motivation for combining the primary and secondary references, and even if there were, there was no likelihood of success that they would work together.

Thus, for the reasons set forth above, reconsideration and withdrawal of this rejection also is respectfully requested.

V. **Conclusion**

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to the effect is earnestly solicited. Should the examiner have any questions regarding the content of this response, a telephone call to the undersigned is invited.

Respectfully submitted,



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